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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/181,601	10/29/1998	STEPHEN ANDERSON	06137-0021-U	1092

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EXAMINER
FREDMAN, JEFFREY NORMAN

ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 09/16/2002 31

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/181,601	Anderson et al
Examiner	**Art Unit**
Jeffrey Fredman	1637

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Jul 30, 2002* .

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under ***Ex parte Quayle***, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-14 and 17* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-14 and 17* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Claim Rejections - 35 USC § 102

1. The rejection of laims 15 and 16 under 35 U.S.C. 102(b) as being anticipated by the Universit of Alabama at Birmingham campus is moot in view of the cancellation of those claims.

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

3. Claims 1, 5, 6 and 11-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wallace et al (Protein Science (1996) 5:1001-1013) in view of Holm et al (TIBS (1995) 20:478-480).

Wallace teaches a method for determining a biochemical function of a protein or

polypeptide domain of unknown function (abstract) comprising: a) identifying a putative polypeptide domain that properly folds into a stable polypeptide domain having a definite three dimensional structure, b) determining the three dimensional structure of the stable polypeptide domain (page 1004-5, subheading "derivation of 3D templates"), c) comparing the determined three dimensional structure to known three dimensional structures in the protein data bank, wherein said comparison identified known homologous three dimensional structures (page 1009, subheading "search for Ser-His-Asp triads in other PDB entries"), d) correlating a biochemical function corresponding to the identified homologous structure to a biochemical function for the stable polypeptide domain (page 1009, figure 5 and page 1011, columns 1 and 2).

The claim does not require that the determination of three dimensional structure occur by a physical step, but broadly includes determinations which simply occur inside the computer algorithm, such as those taught by Wallace.

Wallace teaches identification of domains, but arguably does not teach the use of domains of 50 to 300 amino acids in length for comparison purposes.

Holm teaches determination of three dimensional structures by cyrstallography or NMR (page 478, column 3) followed by database analysis using the complete three dimensional structure of the protein including every amino acid by DALI (page 478, column 3 and page 479). Holm exemplifies a comparison between urease and adenosine deaminase (figure 1) in which the complete three dimensional structrures of the 352 amino acid adenosine deaminase protein is compred to the larger urease protein. Holm further shows a comparison which was performed for the Adenovirus type 5 knob domain (see page 478, table 1) which knob domain represents amino

acids 386 to 581 of the Adenovirus fiber protein, resulting in a comparison of 195 amino acids, within the claim domain size range..

. It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to combine the 3-D structural alignment and function detemination method of Wallace with the NMR and Crystallization techniques, taught by Holm and well known in the art for structure determination purposes and with the use of domains within the range of 50-300 amino acids since Holm teaches screening domains of those sizes. An ordinary practitioner would have been motivated to utilize database analysis of Holm in the method of Wallace since Wallace states "As the number of known protein structures increases, so the need for a 3D equivalent of PROSITE grows with it, especially for likely functions of proteins whose biological role is unknown (page 1001, column 1)". Thus, Wallace expressly notes that there is a need for methods of 3D comparison of proteins in order to determine the biochemical function of unknown proteins. Holm satisfies and answers this need to determine the relatioship of unknown to known proteins. Holm states "At the last stages of solving a new protein structure, crystallographers and nuclear magnetic resonance (NMR) spectroscopists are keen to know if their structure represents a unique protein fold or if it has an unexpected structural similiarity to a known protein fold. To answer these questions, the DALI server performs a database search with a new structure against all structures in the Protein Data Bank. (Page 478, column 3)". Thus, Holm expressly notes that the ordinary practitioner in this art is motivated to perform a comparison to determine the relationship of the new protein with proteins present in the database, thereby fulfilling the stated need and motivation of Wallace.

4. Claims 1-6 and 11-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wallace et al (Protein Science (1996) 5:1001-1013) in view of Holm et al (TIBS (1995) 20:478-480) and further in view of Farber et al (J. Mol. Biol. (1992) 226:471-479).

Wallace in view of Holm teach the limitations of claims 1, 5, 6 and 11-14 as discussed above. Wallace in view of Friedrichs does not teach a prestep of parsing a database to identify the protein coding regions.

Farber teaches a method of discriminating open reading frames (abstract and pages 472-474).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to combine the method of Wallace in view of Holm with the database preparation method of Farber since Farber notes "Simple neural networks predict coding regions in DNA very well when trained on a representation of DNA using single codon frequencies (page 478, column 1)". An ordinary practitioner would have been motivated to combine the method of Wallace in view of Holm with the protein coding determinations of Farber in order to maximize the usable databases to identify homologous proteins and thereby determine the function of unknown proteins.

5. Claims 1, 5-9 and 11-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wallace et al (Protein Science (1996) 5:1001-1013) in view of Holm et al (TIBS (1995) 20:478-480) and further in view of Friedrichs (J. Biomol. NMR (1994) 4:703-726)

Wallace in view of Holm teach the limitations of claims 1, 5, 6 and 11-14 as discussed above. Wallace in view of Holm determines the three dimensional structure of the stable domain

by reference to the protein database and suggests the use of NMR. However, Wallace in view of Holm does not teach the specific NMR characterization techniques nor automated NMR assignments.

Friedrichs teaches determination of the correctness of a protein structure using a variety of NMR spectrometer spectra (page 705) and automated analysis of these spectra using a computer program (pages 708-715). Friedrichs further teaches amide hydrogen exchanges (pages 705 and 708).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to combine the 3-D structural alignment and function detemination method of Wallace with the use of NMR structural determination of Friedrichs since Wallace states "This suggests that the development of databases of 3D templates, such as those that currently exist for protein sequence templates, will help identify the functions of new protein structures as they are determined and pinpoint their functionally important regions (abstract)". Here, Wallace expressly motivates the determination of new protein structures. Motivation to use NMR in this determination is provided by Friedrich, who states "The choice of NMR experiments was based on considerations regarding the sensitivity and resolution of spectra for medium to large-sized proteins (page 720)". Friedrich further motivates the automated assignment of NMR spectra in this determination, noting "Instead of taking weeks, the backbone assignments can be made in one or two days following data acquisition and processing (page 722)". An ordinary practitioner would have been motivated to utilize NMR to determine protein structures in order to sensitively and accurately provide data for 3D determinations and would have been motivated to utilize the

automated assignments of Friedrichs in order to minimize the time needed to determine the 3D structure as expressly motivated by Friedrichs.

6. Claims 1 and 5-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wallace et al (Protein Science (1996) 5:1001-1013) in view of Holm et al (TIBS (1995) 20:478-480) and further in view of Friedrichs (J. Biomol. NMR (1994) 4:703-726) and further in view of Bagby et al (J. Biomol. NMR (1997) 10:279-282).

Wallace in view of Holm and further in view of Friedrichs teach the limitations of claims 1, 5-9 and 11-14 as discussed above. Wallace in view of Holm and further in view of Friedrichs do not teach the button test for microdialysis and NMR.

Bagby teaches a method for preparing samples for NMR to determine optimal solubilization comprising the steps: a) preparing an array of microdialysis buttons with 5 ul containing at least 1 mM protein (page 280), b) dialyzing each member of the array against a different buffer (page 280), c) analyzing the sample to determine if the protein remained soluble (page 280) and d) selecting the optimum solubility for NMR (page 280). Bagby expressly notes a lab expressed the desired protein (page 281, column 2).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to combine the button test of Bagby with the NMR and functional determination method of Wallace in view of Holm and further in view of Friedrichs since Bagby states "The button test is an efficient, small scale way of tackling this problem.(page 281, column 1)". An ordinary practitioner would have been motivated to utilize the button test to optimize solubility for NMR since it is expressly noted as efficient and small scale, which reduced time and

wasted reagents, which for purified proteins can represent a large investment of time and money.

7. Claims 1-9, 11-14 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wallace et al (Protein Science (1996) 5:1001-1013) in view of Holm et al (TIBS (1995) 20:478-480) and further in view of Farber et al (J. Mol. Biol. (1992) 226:471-479)) and further in view of Friedrichs (J. Biomol. NMR (1994) 4:703-726).

Wallace in view of Holm and further in view of Friedrichs and further in view of Farber teach the method of the claims as discussed above. Wallace in view of Friedrichs and further in view of Farber does not teach the use of an integrated system.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use an integrated system because an ordinary practitioner would have been motivated to combine the reagents, software and apparatus used in the methods of Wallace in view of Holm and further in view of Friedrichs and further in view of Farber into an integrated system for determination of protein function from protein structure in order to simplify the determination of protein function by collecting reagents of use in an obvious method into a single location to improve ease of use and minimize effort.

Response to Arguments

8. Applicant's arguments filed July 30, 2002 have been fully considered but they are not persuasive.

Applicant argues that Wallace does not teach identification of domains in the 50 to 300 amino acid range. As noted in the advisory, this argument is not persuasive in view of Wallace's characterization of the Ser195-His57-Asp102 catalytic triad domain (page 1004, column 1), in

which Wallace shows a three dimensional putative polypeptide domain which is composed of at least 195 amino acids (Ser195 being included), which falls within the 50-300 amino acids indicated in the claimed range. Wallace expressly teaches the use of a domain with a minimum size of 196 amino acids.

Applicant then argues the other references do not teach analysis of proteins in the range of 50-300 amino acids. This is incorrect as Friedrichs expressly teaches analysis of proteins which are 94 amino acids in length (see page 718, panel A).

Since the prior art teaches each and every limitation of the claims, the prior art remains applicable and the rejections are maintained.

Conclusion

9. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

10. Any inquiry concerning this communication or earlier communications from the examiner

should be directed to Jeffrey Fredman, Ph.D. whose telephone number is (703) 308-6568.

The examiner is normally in the office between the hours of 6:30 a.m. and 4:00 p.m., and telephone calls either in the morning are most likely to find the examiner in the office.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion, can be reached on (703) 308-1119.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission via the P.T.O. Fax Center located in Crystal Mall 1. The CM1 Fax Center numbers for Technology Center 1600 are either (703) 305-3014 or (703) 308-4242. Please note that the faxing of such papers must conform with the Notice to Comply published in the Official Gazette, 1096 OG 30 (November 15, 1989).

Jeffrey Fredman
Primary Patent Examiner
Art Unit 1655

September 13, 2002